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Risk Factors of Loss to Follow up Among HIV Positive Pediatric Patients in Dar es Salaam, Tanzania

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Abstract

Objective—To identify risk factors for loss to follow up (LTFU) in an HIV-infected pediatric population in Dar es Salaam, Tanzania between 2004 and 2011.

Design—Longitudinal analysis of 6236 HIV-infected children.

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Methods—We conducted a prospective cohort study of 6236 pediatric patients enrolled in care and treatment in Dar es Salaam from October 2004 to September 2011. LTFU was defined as missing a clinic visit for >90 days for patients on ART and for >180 days for patients in care and monitoring. The relationship of baseline and time-varying characteristics to risk of LTFU was examined using a Cox proportional hazards model.

Results—2130 children (34%) were LTFU over a median follow up of 16.7 months (IQR, 3.4–36.9). Factors independently associated with a higher risk of LTFU were age 2 years (RR=1.59, 95% CI 1.40–1.80), diarrhea at enrollment (RR=1.20, 95% CI 1.03–1.41), a low mid-upper arm circumference for age (RR=1.20, CI 1.05–1.37), eating protein 3 times a week (RR=1.39, 95% CI 1.05–1.90), taking cotrimoxazole (RR=1.39, 95% CI 1.06–1.81), initiating onto antiretrovirals (RR=1.37, 95% CI 1.17–1.61), receiving treatment at a hospital instead of a local facility (RR=1.39, 95% CI 1.06–1.41), and starting treatment in 2006 or later (RR=1.10, 95% CI 1.04–1.16).

Conclusions—Health workers should be aware of pediatric patients who are at greatest risk of LTFU, such as younger and undernourished patients, so that they can proactively counsel families about the importance of visit adherence. Findings support decentralization of HIV care to local facilities as opposed to hospitals.

Keywords

Africa; Tanzania; antiretroviral therapy; pediatrics; HIV/AIDS; adherence

Introduction

Patient loss to follow up (LTFU) is a crucial obstacle for successful HIV care and treatment. While evidence indicates that children should be initiated onto antiretrovirals (ARVs) as soon as possible,[1] only 26% of children worldwide requiring treatment are receiving it and many of them are lost at various stages of the HIV treatment continuum.[2] As more countries move to initiate children immediately upon HIV diagnosis, retention after initiation is of paramount importance, particularly so as to reduce resistance to ARVs[3]. Resistance to ARVs develops when patients go on and then off their treatment long enough for the HIV genome to mutate a defense against the drug's effects.[4] Patients can then pass on the drug-resistant strain and those infected die for lack of effective ARVs[5]. Hence, retaining children on treatment becomes important because they could live long lives with ample opportunity to infect others with resistant strains.[6] Currently, improving retention to reduce LTFU of pediatric patients continues to be a challenge in Sub-Saharan Africa (SSA), including in Tanzania.[2]

While children in HIV treatment programs have higher retention rates than adults, a rise in LTFU has been observed as pediatric HIV programs scale up.[7] In Tanzania, research shows that healthier HIV-positive adults, men in particular, are more at risk of LTFU and death, [8,9] whereas research from other SSA countries indicates that the youngest and sicker children, regardless of gender, are more at risk for LTFU.[10–18] SSA studies have also indicated that the child's caregiver and the nearness of their clinic significantly impact the child's adherence to treatment.[19,20] It is important to determine if these findings apply to Tanzanian

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children since research has emphasized the need to tailor retention strategies to those patients most at risk of LTFU. [2,7,21] This study strives to fill the research gap on pediatric LTFU in Tanzania. In addition to analyzing clinical variables, this study also includes socioeconomic and demographic variables that appear to be of increasing importance but have rarely been included in previous studies of risk factors for LTFU among children. Finally, this study analyzes if hospital-based or decentralized care at health centers and dispensaries is associated with increased LTFU.

Methods

Study Population

In 2004 in Dar es Salaam, Tanzania, a joint partnership was formed between Muhimbili University of Health and Allies Sciences, the Dar es Salaam City council, and the Harvard School of Public Health (HSPH) in order to support HIV services in the city. With financial support from the President's Emergency Plan of AIDS Relief (PEPFAR), MDH continues to provide HIV care and treatment support in Dar es Salaam. Between November 2004 and September 2011, MDH enrolled 6579 HIV-infected children (<15 years old) into their program in Dar es Salaam. Clinical and demographic variables were collected on all these patients. Within the 6579 children, 290 of them and their mothers participated in a randomized controlled trial of multivitamin supplementation in Dar es Salaam that occurred between 2004 and 2008.[22] It collected more detailed socioeconomic status (SES) and familial characteristics than were collected through the routine PEPFAR program, so in this subset we were able to look at the effects of SES and familial characteristics in greater depth. A sensitivity analysis was undertaken to ensure that this subset had predictors for LTFU similar to those of the full cohort of children. Ethical clearance for this research was granted by HSPH in Boston and the National Institute of Medical Research (NIMR) in Dar es Salaam.

Study Variables

LTFU was defined separately for patients initiated on antiretroviral therapy (ART) and for patients not yet initiated on ART, also known as in care and monitoring, because ART patients are required to visit the clinic more often to receive their ARVs. Patients on ART were defined as LTFU if their last date of contact with the clinic was >90 days before the date of the administrative end of the study on 30 September 2011 and they were not known to have died or been transferred to another clinic. Patients on care and monitoring were defined as LTFU if their last date of contact with the clinic was >180 days before the date of the administrative end of the study and they were not known to have died or been transferred to another clinic. The definition for LTFU among ART patients is similar to the 2011 WHO working group definition.[23]

Participant specific factors, including demographic, socioeconomic, and nutritional characteristics as well as immunological status, were considered. Standardized weight-for-age (WAZ), height/length-for-age (HAZ), weight-for-height/length (WHZ) Z-scores (for children ≤2 years) and body mass index (BMIZ) Z-scores (for children >2 years) were calculated using the WHO Child Growth Standard reference data.[24] A child was considered

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to be underweight, stunted, or wasted when WAZ, HAZ, or WHZ/BMIZ Z-score respectively was below −2 of the reference population. Z-scores that are considered unphysiologic (>+6 or <−6) were coded as missing.[24] Low mid-upper arm circumference (MUAC) was defined as <11.5cm for children <5 years, <12.9 for children age 5–9 years, and <16.0cm for children age ≥10.[25] Elevated alanine aminotransferase (ALT) was defined as >40 (U/l) for children aged ≤5 years[26] and >30 (U/l) for children >5.[27] Anemia was measured by age-specific hemoglobin level: for children <2 years, hemoglobin <9.5 g/dl; >2–<7 years, hemoglobin <11.0 g/dl; 7–<11 years, hemoglobin <11.5 g/dl; ≥11 years, hemoglobin <12.0 g/dl.[28] Because the ART program did not begin until September 2004, years 2004 and 2005 were combined in the analysis. Years 2006 and 2007 were combined because of pediatric ART guideline changes. Before 2007, for children aged <18 months, eligibility was based on CD4% <20 or WHO stage 3; for children aged ≥ 18 months, eligibility was based on WHO stage 3 or CD4% <15%.[29] After 2007, practices changed and updated guidelines reflect that all children <12 months were initiated regardless of CD4% or WHO stage; for children aged ≥18–59 months, eligibility was based on WHO stage 3 or CD4% <20%; and for children ≥60 months, eligibility was based on WHO stage 3 or CD4% <15%.[30] Cotrimoxazole was given to all exposed babies that continued to breastfeed and to all symptomatic patients with CD4 counts <350 cells per μL or a CD4% <25%.[31] The caretaker variable was defined as either a ‘parent’ or ‘other’, meaning friend, sibling, or extended family member. The household belongings variable was measured as the number of following belongings the patient’s family had in the house and is based on items the Tanzanian government uses to assess SES: a sofa, TV, fan, radio, and refrigerator.[32] Finally the facility-type variable was defined as either a dispensary, healthcare center, or a hospital. Dispensaries provide basic reproductive, child, and outpatient care services, including ART, to between 6000 and 10000 people.[33] Supervising the dispensaries are healthcare centers that serve between 10000 and 50000 people. They provide preventative outpatient care as well as reproductive and minor surgical services.[33] Finally, hospitals serve between 50000 and 1.4 million people and offer outpatient and inpatient services not available at dispensaries or health centers, including laboratory, x-ray, surgical, and emergency obstetric services.[33]

Statistical Analysis

Kaplan-Meier (KM) curves were used to estimate cumulative incidence of LTFU over the study period. The incidence rate for LTFU was calculated from the date of enrollment into the program and 95% confidence intervals (CI) were calculated using the Poisson distribution. The associations between baseline characteristics and LTFU were examined using a Cox proportional hazards model while the associations between time-varying characteristics and LTFU were examined in a separate Cox proportional hazards model. Children were censored when they died, at the end of study in December 2011 if they were event free, or at their last visit date if they were LTFU. Four anthropometric indicators, weight-for-length/BMI Z-score, height-for-age Z-score, weight-for-age Z-score, and MUAC, were examined separately in multivariate regression models because of their high correlations. Relative risks (RR), in particular, hazard ratios, 95% CIs, and corresponding P values were obtained from the models adjusting for multiple covariates. Variables were included in the multivariate models if the estimated RR for their association with LTFU was

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statistically significant at P 0.20 in the univariate analyses[34] or if we reasoned, such as based on literature, that they could be mechanistically related to LTFU.[11,13,35] When potential risk factor data were unavailable, the missing indicator method was used.[36] The criterion for significance for all the analyses was a P value 0.05. All P values were two-sided. Statistical analyses were performed with the statistical software package SAS (version 9.2, SAS Institute Inc., Cary, NC).

Results

From November 2004 to September 2011, 6579 children attended a treatment clinic at least once. Of these, 343 (5.21%) were excluded from the analysis because they never returned to the clinic (or any other MDH clinic) after their first visit. These 343 children would not have been considered part of MDH's program since they did not receive their CD4 results and could not be placed either on ART or in the care and monitoring program. Of the 6236 children eligible for this study, 2130 (34%) were LTFU over 11710 years of follow-up, giving an incidence rate of 18.2 (95% CI 17.4–19.0) per 100 child-years of follow up. The characteristics of the participants at the time of enrollment into MDH are summarized in Table 1. The median age at enrollment was 5 years old and approximately one-half of the children were female. Fifty percent of the participants were WHO stage 3 or 4 and 67% had a CD4 count <350 or a CD4 percentage <20%. Fifty-two percent of children were on cotrimoxazole and 15% had a history of TB infection. Seventeen percent of children had a low MUAC for their age and over a quarter were undernourished as defined by underweight or stunting. Ten percent of children presented with diarrhea and 13% with opportunistic infections. Seventy-three percent of the children's records indicated that their parent was their primary caretaker. Although 54% of the children's families reported spending over 500Tsh (0.32 USD) on food per person per day, 71% reported that the child ate protein >3 times a week.

A summary of participant characteristics associated with LTFU, both baseline and time-varying characteristics, is provided in Table 2. After multivariate adjustment, factors associated with an increase in the risk of LTFU included age ≤2 years (RR=1.59, 95% CI 1.40–1.80), diarrhea at enrollment (RR=1.20, 95% CI 1.03–1.41), a low MUAC for age (RR=1.20, 95% CI 1.05–1.37), taking cotrimoxazole (RR=1.39, 95% CI 1.06–1.81), initiating onto ARVs (RR=1.37, 95% CI 1.17–1.61), receiving treatment at a hospital as opposed to a healthcare center or dispensary (RR=1.39, 95% CI 1.06–1.41), and starting treatment in 2006 or later, where the RRs for LTFU increased log-linearly for each successive year since the program began (p<0.001). The KM curve of LTFU of children who were and were not initiated onto ART at enrollment can be seen in Figure 1 and the KM curve of LTFU of children with and without diarrhea at enrollment can be seen in Figure 2. Although not significant, results also indicated that having a caregiver with positive or unknown HIV status also increased risk of LTFU among children. The association between the SES and familial characteristics are provided in Table 3. After multivariate adjustment, the factor associated with LTFU was eating protein (e.g. fish or meat) at a meal ≤3 times a week (RR=1.39, 95% CI 1.05–1.90). Protein is an expensive food source in Tanzania;[37] therefore, this variable can serve as a proxy for SES and indicates that children from lower SES homes are more likely to become LTFU. A sensitivity analysis

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indicated that the 290 children who had participated in a trial embedded within the overall cohort had similar patient characteristics and the same predictors of LTFU as the larger MDH cohort and that the results of our analysis do not change when this subset is deleted.

Discussion

We identified predictors of LTFU in a cohort of 6236 HIV-positive Tanzanian children who had an incidence of LTFU of 18.2 (95% CI 17.4–19.0) per 100 child-years of follow up. This is similar to studies of other SSA cohorts which have reported incidence rates of 13.6 (11.6–16.1), 18.4 (17.8–18.9), and 26.2 (25.9–26.4) per 100-child years, but smaller compared to a Gambia study's LTFU incidence rate of 115.7 (98.8–137.0) per 100 child-years of follow up.[13] Our study population is one of the largest reported cohorts of HIV-positive children in East Africa for whom clinical, demographic, and SES longitudinal data are prospectively available. An important finding of this study not previously reported was the increased risk of LTFU among children presenting with diarrhea at enrolment. Other important findings were the increased risk of LTFU among children receiving treatment at hospitals as opposed to local facilities and among children ≤2 years.

Although not previously identified in other studies, often because data were unavailable, our study demonstrated that diarrhea at enrollment was associated with an increased risk of LTFU by 20% compared to children without diarrhea. Diarrhea is both a symptom of HIV disease as well as many other childhood infections that contribute to high morbidity and mortality among SSA children.[38,39] A limitation of our diarrhea variable was that it did not indicate if the episode was acute or chronic. In developing countries, diarrhea, specifically chronic diarrhea, is most common among children ≤2 years.[40] In our study, 35% of the ≤2 year olds had diarrhea, a higher percentage than in any other age group. In other SSA settings, cohorts of HIV-infected children ≤2 years report similar proportions of diarrhea incidence while cohorts of non-HIV infected children report lower rates of diarrhea.[41,42] Diarrheal diseases account for >25% of deaths for children <5 in SSA and it could be that the children who had diarrhea at enrollment and who were LTFU in fact died, but we were unable to confirm this.[43] It is also important to note that several studies have found that patients loss to follow-up in ART programmes in SSA are over 3 times as likely to die than patients who remain in care;[44,45] therefore a useful follow up to our study would be to ascertain the mortality rate among patients who become LTFU to be able to better design strategies to prevent both LTFU and otherwise unrecognized mortality.

Children treated at hospitals were at greater risk for LTFU than those treated at local dispensaries even after multivariate adjustment which indicates that the effect is not confounded by sicker children receiving treatment at hospitals. A 2010 study in South Africa comparing LTFU from hospitals versus primary healthcare facilities (PHCs) found that patient outcomes were superior at PHCs, despite PHC-patients having more advanced clinical stage disease when starting ART.[46] This may be because patients do not have to travel as far or to spend as much money to reach PHCs compared to hospitals.[47] Our findings support research from many SSA countries that has found the expansion of pediatric HIV services from tertiary to PHCs has resulted in increased numbers of children on ART and in lower rates of LTFU and mortality.[48–50] Tanzanian policy makers should

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continue decentralizing ART care to local facilities to allow children and their parents' easy access to ART. Young children especially cannot receive treatment if their parents cannot take them to a point of care.

In our study, children ≤2 years were 60% more likely to become LTFU than older children. A recent meta-analysis on the magnitude of LTFU using studies from South Africa, Uganda, Kenya, and Nigeria demonstrated that children ≤2 years were the most likely age group to become LTFU. The two South Africa programs reported they lost 85.1% and 50.2% of infants 12 months after birth respectively while the Ugandan, Kenyan and Nigerian programs reported they lost 53.4%, 66.1%, and 20.8% of infants 18 months after birth respectively.[7] In addition, a study of 258 Malawian children between 2004 to 2006 found that factors significantly associated with LTFU were age <18 months and WHO stage 4,[11] while a study of 441 Gambian children between 2004 to 2010 also found that age <2 years and WHO stage 3 and 4 were significantly associated with LTFU.[13] In our cohort, we suspect but cannot confirm that the significant number of young children LTFU reflects the high mortality rate among exposed children in this age group. Clearly, young patients need to be targeted for treatment and prevention of LTFU in the treatment cascade.

Low MUAC for age at enrollment was associated with increased risk of LTFU in our population, which is consistent with findings that children with poor nutritional status are at increased risk of LTFU in multivariate analyses.[21,38,51] In addition, we found that children who ate protein ≤3 times a week were more likely to become LTFU than children who ate protein >3 times a week. This finding could be interpreted as a sign of poor nutrition as well as a proxy for low SES because protein-rich foods, like meat, are expensive in Tanzania and are primarily consumed by those with high SES.[37,52,53] In addition, meat consumption is unlikely to be confounded by religious identification because pork is rarely consumed in Tanzania generally.[54,55] In support of this hypothesis, children receiving care in Kinondoni district were 22% more likely to become LTFU than their peers in Ilala district, who tend to have higher SES.[56]

The results from several studies are consistent with our findings that pediatric LTFU rates are increasing with increasing calendar time. The West African leDEA group reported that among 2170 pediatric patients, both mortality and LTFU were associated with advanced clinical stage, CD4 percentage <15% at ART initiation, and being initiated after 2005.[10] A 2013 paper from South Africa analyzing 4266 children from 2004 to 2011 also found that risk factors associated with LTFU after 2 years on treatment were age <1 year, initiating ART after 2005, having their mother as their primary caregiver, being underweight (WAZ≤ −2), and low CD4%.[18] Increased risk of LTFU in more recent years is likely due to the increased patient demand for ART services from a limited number of facilities which occurred throughout SSA after that time, with facilities likely being unprepared to handle the large influx of patients.[2]

Published data on the relationship between the caretaker identity e.g. parent, and ART adherence in children has been conflicting;[57] however, recent studies from Zambia and South African have demonstrated that drug adherence is lower among children whose mothers are their primary caretaker, most likely because these women are also HIV positive

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and are therefore sicker and more at risk of dying than their HIV-negative counterparts.[18,58] An HIV positive caretaker could also be afraid of disclosing their child's or their status for fear of discrimination.[20] In our study, univariate analyses demonstrated that the caretaker's identity, parent or other, is not associated with LTFU among children, but children whose caretaker had positive or unknown HIV status were more likely to be LTFU, although this findings was not significant in the multivariate analysis, possibly due to a lack of power. Adherence counseling tailored to the caretaker may be an underappreciated factor affecting treatment outcomes among HIV-infected children living in Tanzania and similar settings.[20]

Although it appears counterintuitive, our finding that children initiated on ART at enrollment are 37% more likely to become LTFU compared to children in care and monitoring is consistent with a 2010 paper evaluating retention of 13510 HIV-infected and exposed children in Western Kenya from 2002 to 2009.[35] It should be noted that the more stringent definition of LTFU is used for those on ART as opposed to those on care and monitoring. Thus, the finding could be, at least in part, a consequence of the differing definition of LTFU between the two groups. It may also appear counterintuitive that cotrimoxazole is a significant predictor of LTFU over time but not at baseline. Currently cotrimoxazole use may be a marker for worsened clinical status; however, although attenuated, the association remained significant even after extensive multivariate adjustment for all measured indicators of clinical status.

The strengths of this study included the large sample size, the prospective nature of the design, and the long follow up (median 16.7 months, IQR 3.4–36.9). Furthermore, since the study was population-based, the findings may be generalizable among HIV-infected children initiating ART in Tanzania as well as in other SSA countries. The limitations to this study are that detailed SES and familial data were available for a relatively small subset of patients. In addition, only 52.9% of the 6236 children had CD4 count data, but this is largely due to Tanzania restricting CD4 count tests to children WHO stage 3 or 4 during the study period because of limited resources.

We found that diarrhea at enrolment, receiving ART at hospitals, age ≤2, and poor underlying nutritional status are important predictors for LTFU in HIV-infected children. It is important from clinical and programmatic perspectives to ensure that treatment programs are aware of these vulnerable groups among children and that there is a mechanism to trace them as soon as possible after a missed clinic visit. In addition, SSA governments should continue to decentralize HIV care and treatment services so that they are easily accessible to patients.

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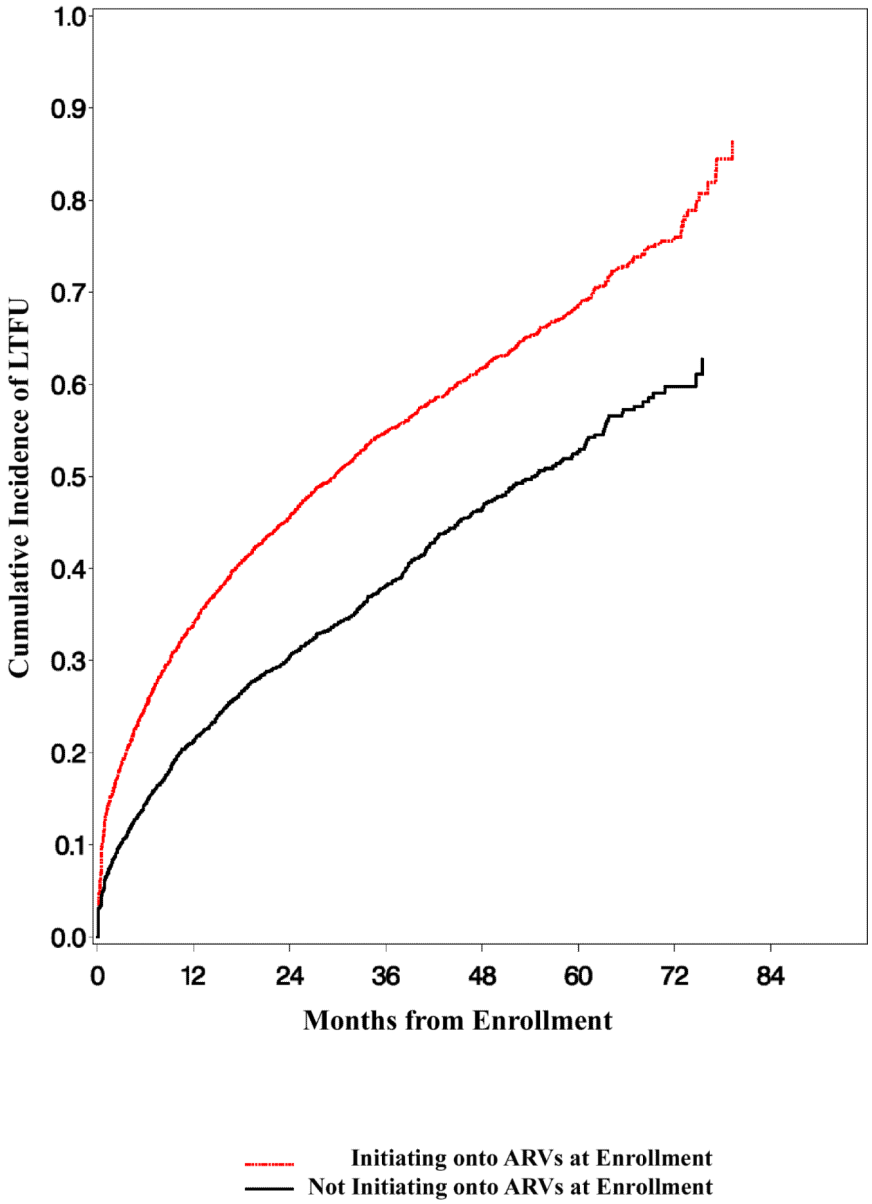

Figure 1.
KM plot of LTFU stratified by Initiated onto ART at Enrolment

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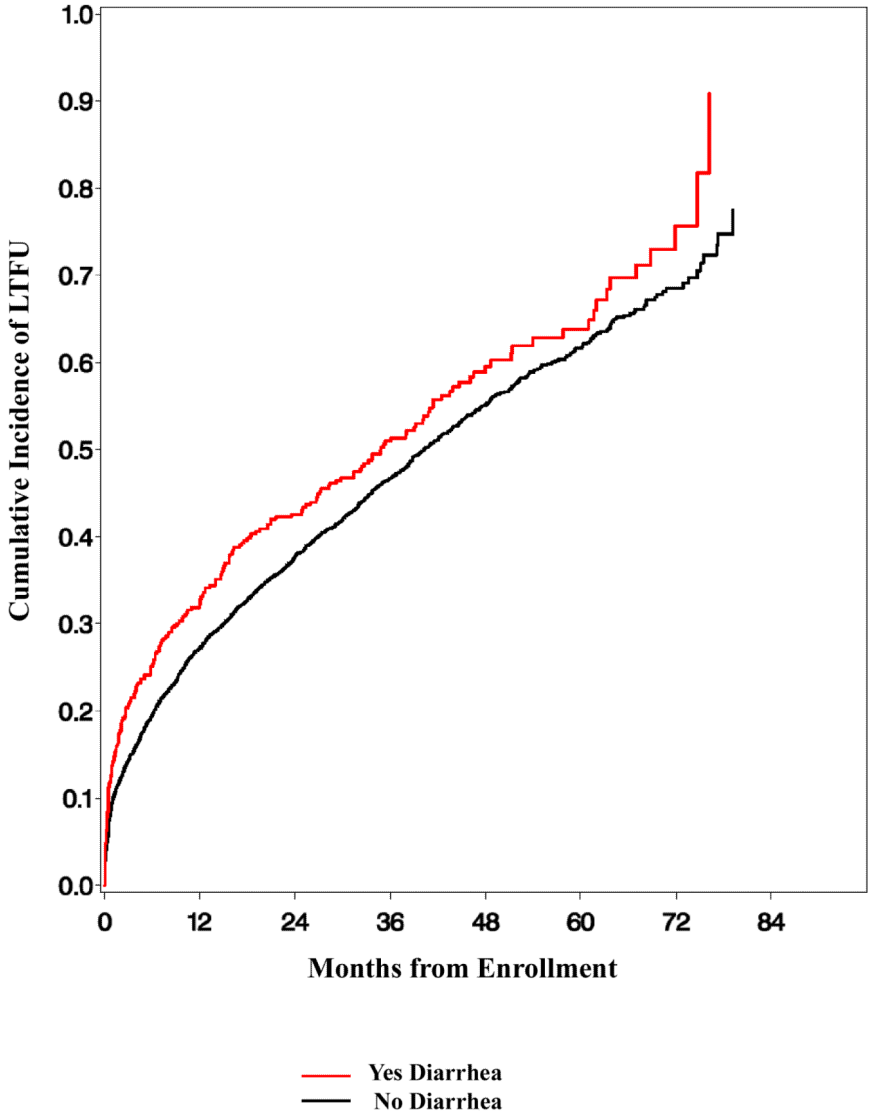

Figure 2.
KM plot of LTFU stratified by Diarrhea at Enrolment

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Table 1

Basic characteristics at time of enrolment (N=6,236)

Characteristics	N(%)
Demographic Characteristics	
Sex	
Male	3,033 (48.6%)
Female	3,203 (51.4%)
Age group, years	
Median(Interquartile Range)	5 (1–9)
≤2	1860 (29.8%)
>2–5	1271 (20.4%)
>5–10	1862 (29.9%)
>10	1242 (15.3%)
District of Residence	
Ilala	2812 (45.3%)
Kinondoni	1801 (29.04%)
Temeke	1589 (25.6%)
Designated Caretaker	
Parent	603 (73.4%)
Other	219 (26.6%)
Parent HIV Status	
Negative	7 (1.3%)
Positive	280 (51.8%)
Unknown	254 (47.0%)
Designated Caretaker's HIV Status	
Negative	14 (1.7%)
Positive	316 (38.5%)
Unknown	491 (59.8%)
Clinical characteristics	
Season of Initiation	
Dec, Jan, Feb, March	1980 (31.8%)
Apr, May	1011 (16.2%)

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Characteristics	N(%)
June, July, Aug, Sept	2209 (35.4%)
Oct, Nov	1036 (16.6%)
Year of Initiation	
2004–2005	590 (9.5%)
2006–2007	2034 (32.6%)
2008	1210 (19.4%)
2009	1048 (16.8%)
2010	847 (13.6%)
2011	507(8.1%)
Facility level	
Hospital	2749 (51.4%)
Center	2277 (42.6%)
Dispensary	320 (6.0%)
MUAC (mm), median (interquartile range)	15.0 (13.0–16.5)
Low mid upper arm circumference[1]	
No	4001(83.3%)
Yes	803(16.7%)
WAZ[2] Score	
WAZ > −1	1103 (29.3%)
−2< WAZ ≤ −1	970 (25.8%)
−3 < WAZ ≤ −2	752 (20.0%)
WAZ ≤ −3	938 (24.9%)
WHZ/BMIZ[3] Score	
WHZ/BMIZ > −1	1955 (49.3%)
−2< WHZ/BMIZ ≤ −1	888 (22.4%)
−3 < WHZ/BMIZ ≤ −2	570 (14.4%)
WHZ/BMIZ ≤ −3	554 (14.0%)
HAZ[4] Score	
HAZ > −1	1202 (27.0%)
−2< HAZ ≤ −1	1065 (23.9%)

[1]Low MUAC is defined as <11.5cm for children <5 years, below 12.9 for children 5–9 years, and <16.0cm for children aged 10+ years.

[2]Underweight is defined as WAZ<-2SD

[3]Wasting is defined as WHZ<-2SD if ≤2 years; BMIZ<-2 SD if >2 years

[4]Stunting is defined as HAZ<-2SD

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Characteristics	N(%)
−3 < HAZ ≤ −2	1069 (24.0%)
HAZ ≤ −3	1115 (25.1%)
WHO stage	
I	1,097 (19.8%)
II	1,667 (30.1%)
III	2,411 (43.6%)
IV	390 (6.5%)
CD4[5] (cells/mm^3)	
<100 OR <12%	1,214 (36.8%)
100 – <200 OR 12% – <14%	284 (8.6%)
200– <350 OR 14% – <20%	726 (22.0%)
350+ OR 20+%	1,073 (32.5%)
Cotrimoxazole	
No	1246 (48.2%)
Yes	1341 (51.8%)
Anemic[6]	
No	1116(27.0%)
Yes	3014(73.0%)
TB history	
No	4,070 (85.3%)
Yes	700 (14.7%)
Diarrhea	
No	4553 (90.1%)
Yes	499 (9.9%)
Elevated ALT[7]	
No	3185 (79.4%)
Yes	829 (20.7%)
Opportunistic Infections	
No	5401 (86.6%)
Yes	835 (13.4%)
Initiated on ARVs at enrollment	

[5]CD4 count, cells/mm^3 OR CD4% if child <12

[6] Anemia was defined as hemoglobin <9.5 g/dl for children <2; hemoglobin < 11.0 g/dl for children 2–<7 years; hemoglobin <11.5 g/dl for children 7–<11; and he

[7]>40 for children aged 5 years or under and >30 for age older than 5 years

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Characteristics	N(%)
No	883 (24.9%)
Yes	2,659 (75.1%)
ARV Regimen (nucleoside/nucleotide reverse transcriptase inhibitor used) at enrollment	
Contains stavudine	676 (29.9%)
No stavudine	1584 (70.1%)
ARV Regimen (Non-nucleoside reverse transcriptase inhibitor) at enrollment	
Contains efavirenz	420 (18.6%)
No efavirenz	1840 (81.4%)
Socioeconomic Characteristics[8]	N=290
Mother's Education in years	
0–7	239 (83.6%)
>7	47 (16.4%)
Mother's Work	
Employed	93 (32.6%)
Not employed	192 (67.4%)
Mother Married	
No	34 (11.9%)
Yes	251 (88.1%)
Father Education[9] in years	
≤7	157 (63.3%)
>7	91 (36.7%)
Number of Adults who eat in home everyday	
0–2	141 (49.3%)
>2	145 (50.7%)
Number of Children <5 years old who eat in home everyday	
0–1	46 (56.1%)
≥2	36 (43.9%)
Daily Food Expenditure of household	
≤500 Tsh or 0.32 USD	53 (19.6%)
>500 Tsh or 0.32 USD	217 (80.4%)

[8]Data is from RCT reported in *Duggan C, Manji KP, Kupka R, et al. Multiple micronutrient supplementation in Tanzanian infants born to HIV-infected mothers: c*

[9]Only known if mother is married

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Characteristics	N(%)
Total Tsh spent on food per person per day	
≤500 or 0.32 USD	124 (45.9%)
>500 or 0.32 USD	146 (54.1%)
Number of times household eats protein a week	
≤3	84 (29.5%)
>3	201 (70.5%)
Household Belongings	
Very low (≤2)	151 (52%)
Low (3)	62 (21.4%)
High (4)	45 (15.5%)
Very high (≥5)	28 (9.7%)

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Table 2

Baseline and Time-varying Demographic and Clinical Characteristics in relation to LTFU: 2130 events, 11710 child-years of follow up

Characteristic	Univariate RR 95% CI	P for trend	Multivariate RR 95% CI	P for trend
Demographic Characteristics				
Sex				
Male	0.99 (0.91–1.07)	0.4525		
Female	Reference			
Age group, years[10]				
≤2	1.62(1.43–1.83)	<0.0001	1.59(1.40–1.80)	<0.0001
>2–5	Reference		Reference	
>5–10	0.75(.66–.86)		0.74(.64–.84)	
>10	0.68(0.58–0.79)		0.66(0.56–0.77)	
District of Residence				
Ilala	Reference	0.03	Reference	0.03
Kinondoni	1.20 (1.09 –1.33)		1.22 (1.10 –1.35)	
Temeke	1.13 (1.02 –1.26)		1.11 (0.99 –1.24)	
Designated Caretaker				
Parent	Reference	0.81		
Other	0.96(0.71–1.29)			
Parent HIV Status				
Negative	Reference	0.073	Reference	0.28
Positive	1.54(0.21–10.87)		1.46(0.20–10.60)	
Unknown	2.33(0.32–16.35)		2.09(0.29–15.04)	
Designated				
Caretaker's HIV Status	Reference	0.031	Reference	0.35
Negative	1.32(0.32–5.37)		1.06(0.26–4.33)	
Positive	1.70(0.42–6.85)		1.43(0.33–5.44)	
Unknown				
Clinical Characteristics				
Season of Initiation				
Dec, Jan, Feb	Reference	.28		
March, Apr, May	0.97(0.93–1.02)			
June, July, Aug,	0.99(0.90–1.16)			
Sept, Oct, Nov	1.05(0.95–1.28)			
Year of Initiation				
2004–2005	Reference	<0.0001	Reference	<0.0001
2006–2007	1.28(1.13–1.46)		1.28(1.07–1.54)	
2008	1.33(1.15–1.54)		1.66(1.36–2.02)	
2009	1.68(1.45–1.96)		2.34(1.90–2.89)	

[10]Only results from time-varying model are shown, but both baseline and time-varying analyses were done.

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Characteristic	Univariate RR 95% CI	P for trend	Multivariate RR 95% CI	P for trend
2010	1.81(1.53–2.14)		2.55(2.04–3.19)	
2011	1.81(1.42–2.30)		2.36(1.77–3.15)	
Facility level				
Hospital	Reference	0.05	Reference	<0.0001
Center	0.69(0.63–0.76)		1.01(0.84–1.21)	
Dispensary	0.42(0.31–0.56)		0.48(0.36–0.65)	
Low mid upper arm circumference[1]				
No	Reference	0.0012	Reference	0.0070
Yes	1.34(1.13–1.60)		1.20(1.05–1.37)	
WAZ Score				
WAZ > −1	Reference	0.003	Reference	0.33
−2< WAZ ≤ −1	0.94(0.81–1.10)		1.00(0.86–1.18)	
−3 < WAZ ≤ −2	0.90(0.76–1.07)		1.04(0.87–1.24)	
WAZ ≤ −3	1.35(1.16–1.57)		1.29(1.08–1.53)	
WHZ/BMIZ Score				
WHZ/BMIZ > −1	Reference	0.70		
−2< WHZ/BMIZ ≤ −1	0.84(0.72–0.99)			
−3 < WHZ/BMIZ ≤ −2	1.04(0.87–1.23)			
WHZ/BMIZ ≤ −3	1.01(0.84–1.21)			
HAZ Score				
HAZ > −1	Reference	0.044	Reference	0.80
−2< HAZ ≤ −1	0.93(0.80–1.09)		1.05(0.90–1.24)	
−3 < HAZ ≤ −2	0.97(0.83–1.13)		1.05(0.89–1.23)	
HAZ −3	1.21(1.05–1.40)		1.24(1.06–1.45)	
WHO stage				
I	Reference	<0.0001	Reference	0.06
II	0.68(0.59– 0.77)		0.83(0.72– 0.95)	
III	0.86(0.76–0.96)		1.05(0.92–1.20)	
IV	1.08(0.88–1.33)		1.20(0.96–1.51)	
CD4[10]				
<100	0.70(0.60–0.80)	<0.0001	0.82(0.70–0.99)	0.11
100 – <200	0.51(0.39–0.66)		0.53(0.40–0.71)	
200– <350	0.61(0.52–0.73)		0.70(0.58–0.84)	
350+	Reference		Reference	
Cotrimoxazole[10]				
No	Reference	<0.0001	Reference	0.002
Yes	1.67(1.29–2.17)		1.39(1.06–1.81)	

[1]Low MUAC is defined as <11.5cm for children <5 years, below 12.9 for children 5–9 years, and <16.0cm for children aged 10+ years.

[10]Only results from time-varying model are shown, but both baseline and time-varying analyses were done.

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Characteristic	Univariate RR 95% CI	P for trend	Multivariate RR 95% CI	P for trend
Anemic, g/dL[10]				
No	Reference	0.1	Reference	0.57
Yes	0.87(0.76–0.98)		0.99(0.86–1.15)	
TB history				
No	Reference	0.37		
Yes	0.94 (0.82–1.09)			
Diarrhea				
No	Reference	0.009	Reference	0.020
Yes	1.34(1.13–1.55)		1.20(1.03–1.41)	
Elevated ALT[10]				
No	Reference	0.95		
Yes	0.98(0.83–1.15)			
Opportunistic Infections				
No	Reference	0.020	Reference	0.27
Yes	1.03(0.99–1.17)		1.08(0.97–1.25)	
On ARVs				
No	Reference	<0.0001	Reference	0.002
Yes	1.56(1.35–1.82)		1.37(1.17–1.61)	
ARV Regimen (nucleoside/nucleotide reverse transcriptase inhibitor used)				
Contains stavudine	0.88(0.72–1.06)	0.14	1.04(0.87–1.24)	0.66
No stavudine	Reference		Reference	
ARV Regimen (Non-nucleoside reverse transcriptase inhibitor)				
Contains efavirenz	4.18(0.98–18.23)	0.06	3.78(0.86–16.61)	0.31
No efavirenz	Reference		Reference	

[10]Only results from time-varying model are shown, but both baseline and time-varying analyses were done.

[10]Only results from time-varying model are shown, but both baseline and time-varying analyses were done.

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Table 3

Baseline Socio-economic Characteristics in relation to LTFU: 180 events, 495 child-years of follow up

Socioeconomic Characteristics	Univariate RR 95% CI	P for trend	Multivariate RR 95% CI	P for trend
Mother's Education				
≤7	1.22(0.82–1.83)	0.49		
>7	Reference			
Mother's Work				
Employed	1.25(0.92–1.69)	0.71		
Not employed	Reference			
Mother Married				
No	0.77(0.48–1.25)	0.82		
Yes	Reference			
Father Education				
≤7	0.77(0.56–1.07)	0.16	0.83(.60–1.15)	0.10
>7	Reference		Reference	
Number of Adults who eat in home everyday				
0–2	Reference	0.53		
>2	0.94(0.70–1.26)			
Number of Children <5 years old who eat in home everyday				
0–1	Reference	0.54		
≥2	0.97(0.55–1.7)			
Daily Food Expenditure				
≤500 Tsh or 0.32 USD	1.30(0.95–1.87)	0.19	1.17(0.81–1.69)	0.97
>500 Tsh or 0.32 USD	Reference		Reference	
Total Tsh spent on food per person per day				
≤500 or 0.32 USD	0.88(0.65–1.19)	0.59		
>500 or 0.32 USD	Reference			
Number of times household eats protein a week				
≤3	1.41(1.04–1.90)	0.21	1.39(1.05–1.90)	0.05
>3	Reference		Reference	
Household Belongings				
Very low (≤2)	1.55(0.87–2.77)	0.72		
Low (3)	1.42(0.76–2.67)			
High (4)	1.39(0.73–2.67)			
Very high (≥5)	Reference			